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Adolescents at Risk for Alcohol Abuse Demonstrate Altered Frontal Lobe Activation during Stroop Performance

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Abstract

Background—Children and adolescents, family history positive (FH+) for alcoholism, exhibit differences in brain structure and functional activation when compared to family history negative (FH-) counterparts. Given that frontal brain regions, and associated reciprocal connections with limbic structures, undergo the most dramatic maturational changes during adolescence, the objective of this study was to compare functional brain activation during a frontally-mediated test of response inhibition in 32 adolescents separated into low-risk (FH-) and high-risk (FH+) groups.

Methods—Functional magnetic resonance (fMRI) blood oxygen level dependent (BOLD) data were acquired at 1.5 Tesla during performance of Stroop Color Naming, Word Reading and Interference. Preprocessing and statistical analyses, covaried for age, were conducted in SPM99 using a search territory that included superior, middle, and inferior frontal gyri (trigone region), anterior cingulate gyrus, and left and right amygdala.

Results—Significantly greater activation in the fronto-limbic search territory was observed in FH+ relative to FH- subjects during Stroop Interference. In addition, a significant regression between brain activation and family history density was observed, with a greater density being associated with increased activation in regions including middle frontal gyrus (BA9) and cingulate gyrus (BA24).

Conclusions—These data demonstrate a significant influence of FH status on brain activation during the performance of a response inhibition task, perhaps reflecting a neurobiological vulnerability associated with FH status that may include reduced neuronal efficiency and/or recruitment of additional neuronal resources. These findings are important given that the adolescent developmental period is already associated with reduced inhibitory capacity, even prior to the onset of alcohol use.

Keywords

frontal lobe; fMRI; FH; alcohol abuse; adolescence

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Introduction

Adolescence is a time notable for brain re-organization, with white and gray matter tissue volumes each undergoing distinctly different patterns of maturation (Giedd et al., 1996; Jernigan et al., 1991; Pfefferbaum et al., 1994; Reiss et al., 1996). Age-related alterations in white matter typically reflect increased myelination, whereas alterations in gray matter reflect neuronal pruning. These progressive and regressive processes are associated with improved cognitive functioning (Casey et al., 2005; Casey et al., 2000; Paus, 2005), perhaps due in part to increased neuronal efficiency (de Graaf-Peters and Hadders-Algra, 2006; Hua and Smith, 2004). While such changes occur in a rapid fashion across many brain regions, areas that include the prefrontal cortex (PFC) demonstrate prolonged structural and functional refinement that continues into the early twenties (Giedd et al., 1999; Gogtay et al., 2004; Luna et al., 2001; Sowell et al., 2001; Sowell et al., 2004; Sowell et al., 2002; Yurgelun-Todd, 2007). Behavioral manifestations associated with frontal lobe development include improvements in executive functioning, such as strategic planning, impulse control, organized search, abstract reasoning, mental flexibility and self-monitoring. These abilities helps to maintain an appropriate mental set that is necessary for adaptive goal-directed behavior (Luria, 1966; Shallice, 1982; Spreen et al., 1995) that contributes to a successful transition from immaturity to independence.

Higher-order cognitive abilities, such as the regulation of inhibitory control, are subserved by a widely distributed and functionally integrated neurocircuitry (Goldman-Rakic, 1988). Accordingly, functional magnetic resonance imaging (fMRI) studies provide evidence for developmental changes in frontal lobe activation during tasks that require response inhibition, such as the Go No-Go task (Adleman et al., 2002; Casey et al., 1997; Luna and Sweeney, 2004; Marsh et al., 2006; Tamm et al., 2002). The Stroop Color-Word Task (Golden, 1976), also used to investigate response inhibition, has demonstrated robust activation of a network that includes anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), middle frontal gyrus (MFG), medial wall frontal regions, middle temporal gyrus, inferior parietal cortex, insula and basal ganglia (Bench et al., 1993; Gruber et al., 2002; Leung et al., 2000; Pardo et al., 1990; Peterson et al., 1999; Taylor et al., 1997). Accordingly, age-related increases in activation of the left lateral prefrontal cortex (PFC) and ACC (Adleman et al., 2002, 7-22 years), and of the right frontostriatal system (Marsh et al., 2006, 7-57 years), have been reported during Stroop Interference. Thus, the immature yet rapidly developing frontal lobe serves as an inherent neurobiological vulnerability during adolescence, particularly when cognitive demands are high, that could affect navigation of decision-making challenges and the capacity to avoid risky or inappropriate behavior, suboptimal response selection or performance, or harmful consequences.

The onset of alcohol and illicit substance use typically occurs during this period of critical adolescent brain development (Bates and Labouvie, 1997; Johnston et al., 2000). It is known from studies in adult populations that heavy alcohol consumption is associated with deficits across several domains of cognition (Parsons and Nixon, 1998), with executive functioning and memory being the most vulnerable to disruptions by alcohol (Fillmore et al., 2005; Goudriaan et al., 2007; Hartley et al., 2004; Marczinski et al., 2007; Sher et al., 1997; Townshend and Duka, 2005; Weissenborn and Duka, 2003). MRI and fMRI studies have revealed alcohol-related alterations in brain structure (Jang et al., 2007; Paulus et al., 2006; Pfefferbaum et al., 1997; Sullivan and Pfefferbaum, 2005) and brain activation during performance of cognitive tasks (Tapert et al., 2004a; Tapert et al., 2001). While previous studies have likewise documented consequences of adolescent alcohol use on brain structure and cognitive function (Brown et al., 2000; De Bellis et al., 2005; Nagel et al., 2005; Tapert et al., 2004b), it is unclear whether these structural and functional abnormalities are

antecedent to the initiation of alcohol use or are the consequence of alcohol use during adolescent brain development.

In order to address this question, previous studies have compared adolescents who are family history positive (FH+) for alcoholism, and who have no or minimal alcohol exposure, with age-matched family history negative (FH-) non-using counterparts. This is an important population to examine, as a positive family history of alcoholism is associated with an earlier initiation and greater magnitude of use (Biederman et al., 2000; Chassin and Barerra, 1993; Clark et al., 2005; Hill et al., 2000; McGue et al., 2001), and a greater prevalence of alcohol use disorders in adolescents and young adults (Chassin et al., 2004; Lieb et al., 2002; Milberger et al., 1999). Although intellectual functioning falls within the average range (Alterman et al., 1989; Johnson and Rolf, 1988; Schuckit et al., 1987), children of alcoholics demonstrate deficits in abstract reasoning and planning, lower IQ scores, and poorer spelling and math performance compared to children of non-alcoholics (Poon et al., 2000). Poorer academic performance has also been reported in at risk adolescents (McGrath et al., 1999; Murphy et al., 1991; Reich et al., 1993; Silveri et al., 2004; Silveri et al., 2008; Vitaro et al., 1996). MRI studies have shown that while whole brain gray and white matter tissue volumes do not differ between FH+ and FH- youth (Silveri et al., 2008), FH+ youth demonstrate reduced amygdalar volumes (Hill et al., 2001), larger cerebellar volumes (Hill et al., 2007b), and reduced right/left orbitofrontal volumes (Hill et al., 2009), relative to FH- youth. Taken together, these studies conducted in FH+ youth suggest evidence for cognitive and neurobiological vulnerabilities associated with increased risk for developing an alcohol abuse problem later in life.

Data from fMRI studies of FH+ children and adolescents are more limited. While no performance differences were observed between FH+ and FH- groups during a spatial working memory (SWM) task, FH+ youth exhibit greater BOLD activation in superior frontal lobe regions during rest and less BOLD activation in the cingulate gyrus (CG) during a simple vigilance condition (Spadoni et al., 2008). Functional activation differences reported for the Go No-Go task demonstrate that FH+ adolescents exhibit less activation in the left MFG relative to FH- counterparts (Schweinsburg et al., 2004). To date, no fMRI studies have compared brain activation in FH+ and FH- youth during performance of the Stroop Color-Word task, thought to be more demanding and effortful than the Go No-Go task due in part to the involvement of conflict monitoring and resolution during task performance (Spreen et al., 2006), and perhaps task-specific differences in functional integration of multiple brain regions (Leung et al., 2000; Pardo et al., 1990; Peterson et al., 1999). Thus, the objective of the current fMRI study was to test the hypothesis that FH status has a significant influence on frontal lobe activation during performance of Stroop Interference, by comparing adolescents stratified into high-risk (FH+) and low-risk (FH-) groups.

Materials and Methods

Participants

The study sample consisted of 32 healthy adolescent volunteers, recruited from the local surrounding communities via advertisement and word of mouth. The overall sample was 59% female, 88% Caucasian (6% African American, 6% Hispanic), typically from middle-upper class socioeconomic status (Hollingshead, 1957), and with a mean age of 13.4 ± 2.9 yrs. (mean ± SD; age ranging from 8 to 19 yrs. old) and a mean education of 7.5 ± 2.8 yrs. (education ranging from 3 to 12 years). The accompanying parent, almost exclusively the mother, underwent a Family History – Epidemiologic (FHE) structured interview to obtain information about the parents and children, as well as an unstructured family interview to obtain information about second-degree relatives. Information from parental interviews was

used to stratify subjects by family history status (low risk (FH-) or high risk (FH+)). Subjects met the criteria for FH+ status if there was a positive parental report of either parental or grandparent alcohol abuse (28%, 61% of the sample, respectively) or both parental and grandparent alcohol abuse (11% of the sample). Family expression of alcoholism, or family history density (FHD) of alcoholism, as determined using methods established by Zucker and colleagues (Zucker et al., 1994), was also calculated for each subject, where a single parent with a history of alcoholism contributes 0.5 and a single grandparent contributes 0.25 to the total score, for a possible range of 0 (FH-) to 2 (0.25 – 2.0, FH+). Previous work suggests that FHD may be more sensitive for determining the influence of familial alcohol use disorders than categorical approaches (Stoltenberg et al., 1999). According to these criteria, the FH+ group was comprised of 18 adolescents (family density = 0.43 ± 0.28) and the FH- group was comprised of 14 adolescents (family density = 0.0 ± 0.0). As determined by the family history interview, no cases of premature birth or maternal alcohol or drug use were reported among the enrolled study participants. Demographic data from the study subjects, which did not differ significantly between groups, are presented in Table 1.

Procedure

All aspects of the clinical research protocol were reviewed and approved by the Institutional Review Board of McLean Hospital (Belmont, MA, USA). After a complete description of the study, all subjects and their parent(s) or guardian(s) provided written informed assent and consent, respectively, prior to participation. Subjects received monetary compensation for participating in the study.

Clinical Assessment

A trained psychologist conducted diagnostic interviews and clinical assessments. Subjects underwent a structured clinical psychiatric interview, using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E, (Puig-Antich et al., 1980), to rule out Axis I pathologies according to the Diagnostic and Statistical Manual IV (DSM) (e.g., depression, bipolar illness, schizophrenia, conduct disorder, attention deficit disorder). All participating subjects were free of psychiatric diagnoses, neurological illness, severe medical problems, and current or >3 lifetime episodes of alcohol or drug use.

Functional Magnetic Resonance Imaging Protocol

Functional images were acquired for the whole brain on a 1.5 Tesla General Electric Signa LX magnetic resonance scanner (General Electric Medical Systems, Milwaukee, WI), equipped with a birdcage quadrature RF head coil, using echo planar imaging (EPI) blood oxygen level dependent (BOLD) fMRI. Three set of images were generated: a T1-weighted sagittal localizer (spin echo, 256 × 192, 1 NEX, 24 slices, SLT=4mm with a 1-mm gap, TE=19msec, TR=600msec), a dual echo T2-weighted axial series (VEMP, 256 × 192, 0.5 NEX, 54 slices interleaved, SLT=3mm, TE=30/80msec, TR=3000msec) and 3) 3-D fourier transformed spoiled gradient-recalled acquisition images (SPGR, 256 × 192, 124 slices, 1 NEX, SLT=1.5mm, TR=35msec, TE=5msec, flip angle=45°). A neuroradiologist reviewed the clinical images of each subject to rule out neurological structural abnormalities. Sagittal scout images were acquired for alignment and localization using a fast spin echo sequence (FSE) with the following imaging parameters: repetition time (TR) = 3 msec, echo time (TE) = 40 msec, field of view (FOV) = 20cm, matrix size = 64 × 64, slice thickness = 7 mm (1mm gap), and flip angle = 90°. Visual stimuli were projected onto a translucent screen located at the foot of the scanning bed via a magnetically shielded LCD video projector and observed through a mirror mounted on the head coil.

In order to minimize motion associated with vocalization of responses, foam cushions were inserted between the subjects' head and the quadrature head coil for a snug fit. Subjects were fitted with tape across the forehead and chin during landmarking, and head position was rechecked prior to removal from the scanner. While these methods do not reduce fine motion associated with localizing a response, the amount of gross movement is minimized.

Stroop Color-Word fMRI Paradigm

Adolescents completed a version of the Stroop Color-Word Interference Task while undergoing EPI BOLD fMRI. Detailed descriptions of this paradigm have been published previously (Gruber et al., 2002; Killgore et al., 2007). The Stroop test challenges the ability to inhibit inappropriate responses and resist interference using the following conditions: Color Naming (name the color of the block); Word Reading (read words printed in black ink); Interference (name the color of the ink when words are printed in an incongruent color). In a blocked paradigm, each task was completed in a series of three 2.5 min scans. Color Naming consisted of a series of 10 screens each presenting a line of six red, green, and blue colored rectangles (2500 ms stimulus; 500 ms inter-stimulus interval). Word Naming consisted of a series of 10 screens each presenting a line of text comprising six randomly ordered words of “red”, “green”, and “blue” printed in black ink (2500 ms stimulus; 500 ms inter-stimulus interval). Given the longer duration of time required to complete the Color-Word Interference condition, six screens each presented a line of text comprising six printed words of “red”, “green”, and “blue” printed in an incongruent color (4500 ms stimulus; 500 ms inter stimulus interval). This timing sequence was established previously by determining the average reaction time for the completion of six targets in each condition in healthy adult subjects tested off-line (Gruber et al., 2002). Each scanning epoch consisted of five alternating 30s periods (total length, 150s), in which two trials of one Stroop condition were alternated with three rest periods consisting of a simple fixation point (e.g., rest, Color Naming, rest, Color Naming, rest).

Subjects were required to communicate vocal responses via microphone for each series (screen) of each condition (Color Naming, Word Reading and Interference) of the Stroop task. A technician recorded the number of targets incorrectly identified (errors) for each component of the Stroop task, with performance being evaluated by averaging number of errors and percent accuracy over the two trials, within a block of the fMRI paradigm. This yielded a maximum score of 60 (100%) on 10 trials of 6 color blocks (Color Naming), 60 (100%) on 10 trials of 6 words (Word Reading), and 36 (100%) on 6 trials of 6 words written in an incongruent color (Interference).

Image Processing and Data Analysis

Preprocessing and statistical analyses were conducted in SPM99 (Friston et al., 1995) using Matlab (The Mathworks Inc. Sherborn MA, USA). The functional data sets were motion corrected (intra-run realignment) within SPM99 using the first image as the reference. Data that exceeded 2 degrees or 2 millimeters in either the rotational or translational plane was excluded from the analyses. No participants were excluded on this basis. Average motion correction for each subject for each translational and rotational plane was between 0.5 and 1.5mm and 0.5 and 1.5 degrees, respectively, with no differences in average motion being observed between FH+ and FH- groups. After realignment, the image data were normalized to a standard template from Montreal Neurological Institute (MNI) with an isotropic 2×2×2 mm voxel size and smoothed using an isotropic Gaussian kernel (full width half maximum [FWHM] = 10 mm).

The analysis followed a two-step random effects approach in SPM99 in order to permit inference to the population from which the data were collected (Penny et al., 2003). First, a

150-second box-car waveform, convolved with hemodynamic response function, was used as the reference paradigm. Using general linear model and the hemodynamically-corrected reference paradigm, T-score values were calculated for each voxel. Contrasts were set to test for voxel-wise effects of signal differences between conditions, [Color Naming - Fixation], [Word Reading - Fixation], and [Interference-Fixation] - [Word Reading – Fixation], [Interference-Fixation] - [Color Naming-Fixation], and statistical parametric maps (SPM{t}) were calculated for each subject. The following abbreviations are used throughout to represent the aforementioned contrasts, respectively: Color Naming, Word Reading, Interference – Color Naming and Interference – Word Reading.

The whole group (both FH+ and FH- subjects) was first examined for each contrast, and then in the second stage, contrast images were used to compare activation differences between FH+ and FH- adolescents. A region of interest (ROI) approach, as described previously (Killgore et al., 2007), was used for all fMRI analyses. The ROI was restricted to a search territory that included superior, middle, and inferior frontal gyri (trigone region), the ACC, and the left and right amygdala, as defined by a published anatomical atlas (Tzourio-Mazoyer et al., 2002), and as implemented in the Wake Forest University PickAtlas Utility (Maldjian et al., 2003). Regions within this fronto-limbic search territory were selected given their reciprocal connections (Bracht et al., 2009; Stein et al., 2007), and were based on previous fMRI and MRI studies documenting involvement in response inhibition (Leung et al., 2000; Pardo et al., 1990) and error detection (Polli et al., 2008; Polli et al., 2009), as well as structural differences observed in FH+ youth (Hill et al., 2001; Hill et al., 2009). Regions of activation within the ROI were evaluated at an uncorrected threshold of $p < .001$, with the k (extent) = 20 contiguous voxels. ROI analyses were corrected for multiple comparisons using family-wise error rate implemented within SPM99 using the Pickatlas utility. Significant activations within the ROI at an uncorrected threshold of $p < .001$ that also survived multiple comparisons corrections at $p < .05$ are indicated in Tables 3-5. Activation images were superimposed on an average template brain normalized to the standardized coordinate space of the Montreal Neurological Institute (MNI) for visualization. To identify anatomical locations, MNI coordinates were converted to Talairach space using the icbm2tal transform in GingerALE Version 2.0 (http://www.brainmap.org/ale/index.html), and entered into Talairach Daemon Client Version 2.4.2. (Lancaster et al., 2000). Contrast images presented in Figures 1 and 2 were formatted using MRICron (www.cabiatl.com/mricro/mricro/index.html).

Performance data (number of errors and percent accuracy) for the Color Naming, Word Reading and Interference components of the Stroop task were examined between FH+ and FH- adolescent using a one-way analysis of variance (ANOVA) using SPSS 11.0 (SPSS, Chicago, IL), with α set at .05. No significant group differences or correlations with FHD were observed for performance data on any of the three components of the Stroop task (Table 2).

Results

Whole Sample ROI Analysis

ROI analysis of the whole study sample (n=32), with age included as a covariate, revealed activation patterns for Color Naming and Word Reading contrasts that included bilateral precentral gyrus (PG) and insula, left MeFG, and right CG (Table 3), with Word Reading also including additional activation in the BA9 region of the left MeFG (Table 3).

The Interference – Color Naming contrast for the whole study sample demonstrated additional activation in the left MFG, left MeFG, right PG and the right ACC, whereas the

Interference – Word Reading contrast demonstrated increased activation in the left PG and left MFG as compared to the Color Naming and Word Reading tasks alone (Table 3).

Categorical Family History Effects

No significant FH activation differences were observed during Color Naming, however during Word Reading, FH+ subjects activated significantly more regions of the search territory, including bilateral ACC, bilateral MFG and left IFG than FH- subjects (Table 4). Although no FH differences were observed when the Interference – Word Reading contrast was examined, significant differences were evident for the Interference – Color Naming contrast. As reported in Table 5, the FH+ group demonstrated significantly greater activation in bilateral MFG, left insula, right ACC, and left MeFG relative to FH- counterparts, whereas FH- subjects demonstrated only increased activation in the PG as compared to the FH+ group.

FHD Regression Analyses

Regression analyses conducted for the calculated FHD measure and brain activation for the Interference – Word Reading and Interference – Color Naming contrasts revealed significant relationships. For the Interference – Word Reading contrast, greater family density was associated with enhanced activation in the right ACC, right MFG, left superior frontal gyrus (SFG) and right PG (Table 6). An illustration of the positive regression of FHD as a function of brain activation for Interference – Word Reading at the local maxima in the right ACC (x=6, y=37, z=11) is presented in Figure 1.

For the Interference – Color Naming contrast, greater family density was associated with enhanced activation in the left and right MFG, left SFG, left CG, left insula and right PG (Table 7). An illustration of the positive regression of FHD as a function of brain activation for Interference – Color Naming at the local maxima in the right MFG (x=26, y=11, z=44) is presented in Figure 2.

Significant negative correlations were also observed, with a greater FHD being associated with less activation in the right SFG for Interference – Word Reading (Table 6) and left SFG, left PG, and right MeFG for Interference – Color Naming (Table 7).

Error Rate Regression Analyses

Regression analyses conducted for Interference error rate and brain activation for the Interference – Color Naming contrast revealed a significant positive relationship, with increased error rate being associated with greater activation in the left MFG (BA46, 28 voxels, local maxima x=-46, y=30, z=23, SPM {t} = 3.98). A significant negative regression was not observed. When the regression of error rate and brain activation was conducted separately for each FH group, significant positive regressions were observed for left SFG (BA10, 29 voxels; x=-27, y=49, z=26; SPM {t} =4.09) and left MFG (BA46, 84 voxels; x=-46, y=30, z=24; SPM {t} =4.06) in the FH- group, however, no significant areas of activation that correlated with error rate were observed for the FH+ group.

Discussion

The current findings are consistent with previous Stroop fMRI studies demonstrating activation of a network of frontal lobe regions during performance of the Interference condition (Gruber et al., 2002; Leung et al., 2000; Pardo et al., 1990; Peterson et al., 1999). With age included as a covariate, the contrast of Interference – Color Naming revealed a network of brain activation that was unique from that observed during Color Naming, Word Reading, and Interference – Word Reading. Both Interference contrasts demonstrated

increased recruitment of the PG, but also additional engagement of the PFC (BA9, involved in executive functions and cognitive control) and dorsal ACC (BA32, involved in decision-making) for Interference – Color Naming and increased activation of the DLPFC (BA 46, involved in executive functions) for Interference – Word Reading. These results confirm that in the current sample of adolescent subjects, performance of a cognitive task requiring response inhibition, Stroop Interference, is subserved by enhanced recruitment of frontal lobe neurocircuitry that is unique from the Color Naming and Word Reading subtests alone.

The current results also support the hypothesis that FH status has a significant influence on brain activation during Stroop Interference. Although no FH effects were observed for Color Naming, the Interference – Color Naming contrast demonstrated greater activation within the region of interest in FH+ adolescents relative to FH- counterparts. Regardless of whether a categorical approach comparing FH+ versus FH- subjects or a regression analysis including FHD (Zucker et al., 1994) was used, areas within the search territory exhibiting greater activation during Stroop Interference in FH+ youth included BA6, BA8 and BA9, and left insula. Activation of these regions of the premotor cortex (BA6/8) and PFC (BA9) has been reported previously in fMRI studies of Stroop Interference (Adelman et al., 2002; Leung et al., 2000; Peterson et al., 1999). Activation of the insula has also been reported previously during Stroop Interference (Leung et al., 2000). Both approaches revealed enhanced recruitment of the cingulate cortex in FH+ youth, however, the categorical approach revealed greater activation in the right ACC (BA32) and the FHD regression approach revealed greater activation in the left CG (BA24). The ventral cingulate cortex (BA24), which is part of the limbic system that has connections to the amygdala, hippocampus and orbito-frontal cortex, and dorsal ACC (BA32), which is involved in decision-making, have been implicated in Stroop performance. No categorical group differences were observed for the Interference – Word Reading contrast, however, the FHD regression analysis demonstrated that a denser family history was associated with greater activation in the ACC, MFG, SFG, and PG, and less activation in the BA6 region of the SFG.

While the Interference – Color Naming contrast provided evidence for increased neurobiological recruitment associated with response inhibition that is dissociable from color naming ability between FH groups, the Interference – Word Reading contrast provided supporting evidence for increased recruitment specific to response inhibition, albeit not as clearly dissociable from FH effects associated with word reading ability. It is noteworthy that greater activation in the ACC, dorsal (BA32) and ventral (BA24) portions, and bilateral MFG (BA9/46) and IFG was observed in FH+ youth during the simple Word Reading component of the Stroop task. This pattern of altered activation was of a lesser magnitude when compared to the FH-related alterations observed for Interference (relative to Color Naming or Word Reading), but could nonetheless reflect a developmental vulnerability in neuronal resource allotment during a simple information-processing task that is considered to have a high degree of automaticity (Protopapas et al., 2007). These surprising findings should be interpreted cautiously, particularly given a lack of FH differences in activation during the simple Color Naming condition, and in light of similar task performance between groups.

Enhanced recruitment of brain regions in FH+ youth is consistent with reports that compensation of brain activity (increased BOLD signal) occurs in the affected and adjacent regions, when a region of the brain is temporarily fatigued or otherwise compromised, in order to sustain roughly equivalent levels of performance on cognitively demanding tasks (Chang et al., 2008; Drummond et al., 2005; Gruber et al., 2002; Kanayama et al., 2004). Taken together, these findings suggest evidence for increased neuronal recruitment in FH+ youth during performance of a response inhibition task, despite the absence of significant

performance differences between groups. There was some modest evidence for a significant regression between error rate and greater activation of the left MFG (BA46) and left SFG (BA10), however this relationship was driven by FH- youth. This is consistent with findings observed by Marsh and colleagues (Marsh et al., 2006), who reported a significant correlation between increased activation in the BA10/46 regions and poorer performance on Stroop Interference.

The findings in this report contrast with the findings from Schweinsburg and colleagues (Schweinsburg et al., 2004), who reported significantly less frontal lobe activation in FH+ adolescents relative to FH- counterparts during Go No-Go performance. These conflicting results are not surprising, as performance of these tasks require unique response components that are task-specific, e.g., Go No-Go requires withholding a motor response, whereas the Stroop Interference task used in this study requires vocalizing a less automatic response (naming ink color) while inhibiting a more automatic tendency (reading words). Differential activation of neural circuits between FH groups may therefore not generalize across response inhibition tasks that require different sensory or response demands (Stevens et al., 2007). These findings highlight the necessity of utilizing different challenge paradigms in order to identify elements of response inhibition that might be mediated by a common neural network, as well as differences in network dynamics that vary as a function of cognitive demand. It is plausible that frontal lobe activation is influenced by FH status, indicating that FH+ youth experience a neurobiological change on a network level, in the absence of performance differences.

There are a number of factors that must be considered when interpreting these study findings. First, while the current investigation includes a moderate sample size for neuroimaging studies, the sample size provided limited power for the investigation of sex effects on functional brain activation. Future studies should address the potential interaction between FH status and sex, particularly in light of the reports of significant sex differences in brain structure and function during adolescence (Gallagher et al., 2000; Halpern, 1992; Silveri et al., 2004; Silveri et al., 2006; Silveri et al., 2008; Yurgelun-Todd et al., 2002). The sample was well characterized, in that all adolescent subjects in this study reported less than three episodes of lifetime alcohol use and no lifetime use of other psychoactive substances, had middle to upper class SES status, regardless of FH status, and did not meet criteria for psychiatric conditions such as attention deficit disorder or conduct disorder. Furthermore, inclusion of age as a covariate in all SPM analyses likely minimized the possibility that FH group differences were influenced by age (given an age range of 8 to 19), which could be associated with the developmental time course of frontal lobe maturation. Although there are inherent limitations associated with the fMRI block design (Amaro and Barker, 2006), Leung and colleagues (Leung et al., 2000) have reported similar, albeit less robust, activation in frontal brain networks during Stroop performance when using a block design in comparison to an event related design.

Risk associated with FH status may have been minimized as a result of the methods used to establish a family history of alcohol abuse. Our categorization was based on a structured interview with a single parent, a method that has been shown to be less sensitive for detecting accurate family history status than interviewing multiple family members (Rice et al., 1995). Furthermore, the majority of adolescents in the FH+ group were from simplex families with alcohol dependence, that is, families where only a single relative, parent or grandparent, was identified as meeting the criteria for a positive family history of alcohol dependence (88%). It has been suggested by Hill and colleagues (Hill et al., 2007a), that a greater family loading of alcoholism (multiplex family history of alcoholism) is associated with a greater genetic susceptibility for developing an alcohol use disorder. Our sample therefore would be expected to have a lesser genetic loading than subjects drawn from

multiplex families and, as a result, would be expected to exhibit more subtle activation differences. Importantly, complementary FH results were observed in the present study when both categorical and FHD (Zucker et al., 1994) regression approaches were employed to examine the influence of FH effects on brain activation during Stroop Interference.

Within the framework of characterizing brain reorganization and rapid improvements in cognition during the adolescent period, studies identifying structural, functional and cognitive deficits in adolescents with high- versus low-risk for future alcoholism suggest a potential neurobiological vulnerability that may be present prior to the initiation of alcohol use (Hill et al., 2007b; Schweinsburg et al., 2004; Silveri et al., 2008; Spadoni et al., 2008). While the adolescent developmental period is already associated with reduced inhibitory capacity, having a positive family history may confer risk for future alcoholism by impacting adolescent maturation of frontal networks which is necessary to develop the capability to evaluate and appropriately modulate response inhibition, as well as emotional responses (Luna and Sweeney, 2004; Rubia et al., 2000; Yurgelun-Todd, 2007). Resulting difficulties with cognitive control could therefore place FH+ adolescents at even greater risk when faced with decision-making challenges that include when to begin drinking alcohol, which is well established to influence the escalation of alcohol consumption and risk for developing an alcohol abuse disorder later in life (Brown and Tapert, 2004; Chassin et al., 2004; Grant and Dawson, 1997; Hill et al., 2000).

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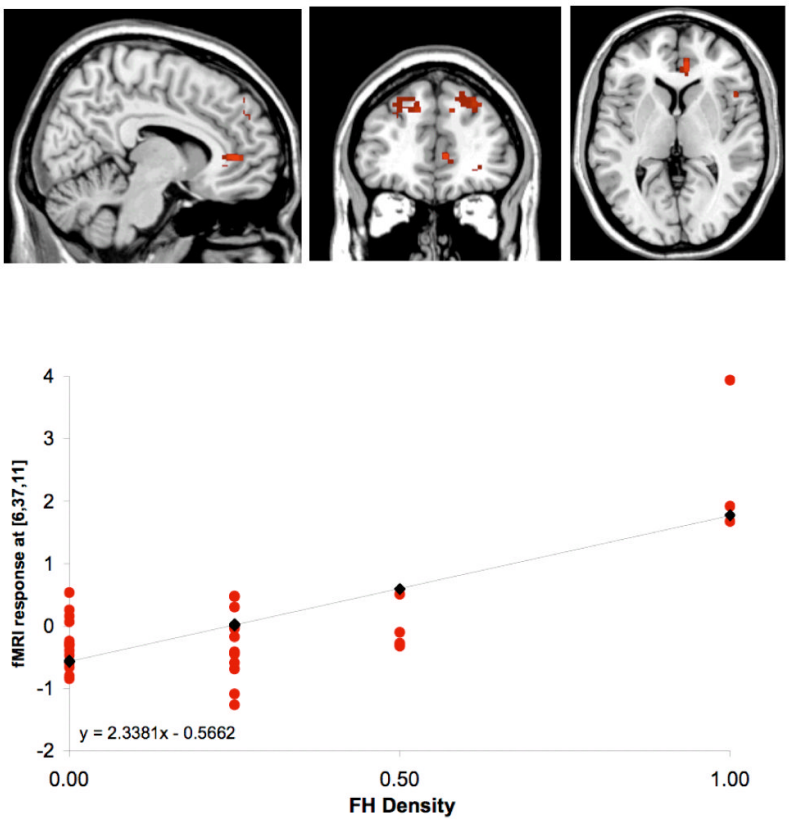

Figure 1. FHD Regression with Brain Activation for Interference – Word Reading

Illustration of SPM maps demonstrating the significant positive regression ($p<.05$) between greater FHD and greater activation during the Interference condition of the Stroop task [Interference – Word Reading]. Local maxima coordinates were x=6, y=37, z=11, with 75 activated voxels, SPM {t} = 5.49, significant at small volume corrected threshold, p<.05, and containing right ACC (BA32). L, left hemisphere; R, right hemisphere. Red circles represent individuals subjects and black diamonds represent average activation for each FHD group.

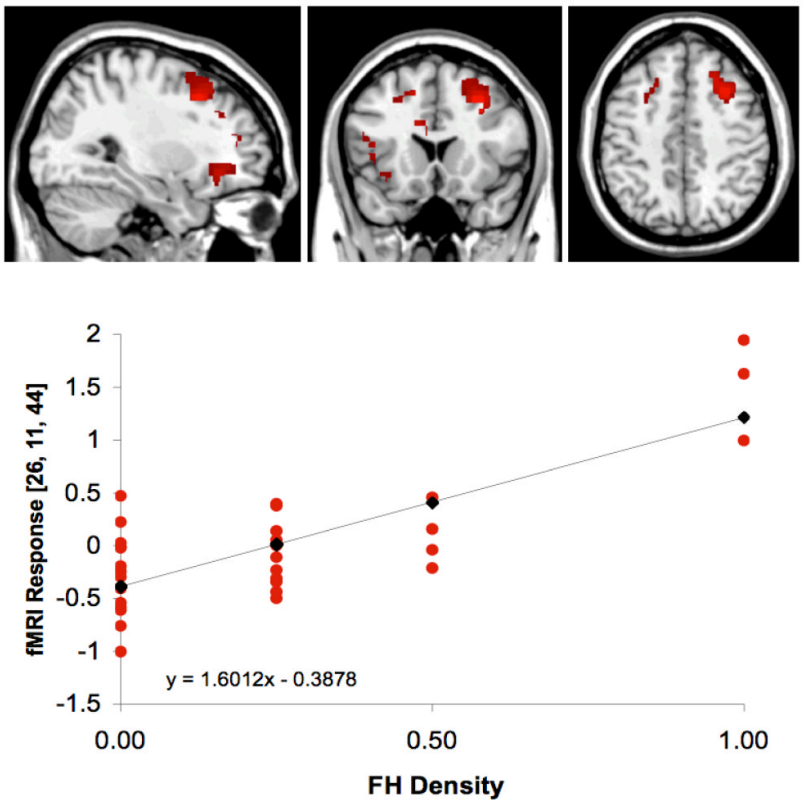

Figure 2. FHD Regression with Brain Activation for Interference – Color Naming

Illustration of SPM maps demonstrating the significant positive regression (p<.05) between greater FHD and greater activation during the Interference condition of the Stroop task [Interference – Color Naming]. Local maxima coordinates were x=26, y=11, z=44, with 1108 activated voxels, SPM {t} = 6.64, significant at small volume corrected threshold, p<. 05, and containing right MFG (BA8). L, left hemisphere; R, right hemisphere. Red circles represent individuals subjects and black diamonds represent average activation for each FHD group.

Table 1

Subject Demographics

	FH+ (n=18)	FH- (n=14)	*p*
Age	13.2 ± 3.2	13.8 ± 2.6	.59
Female	57%	61%	-
Education	7.3 ± 3.0	7.8 ± 2.6	.53
Handedness	17R, 1L	14R, 0L	-
Ethnicity	93% Caucasian	83% Caucasian	-
Family History Density	0.43 ± 0.28	0.00 ± 0.00	.0001

Data represent mean scores. ± SD.

Table 2

Stroop Performance

	FH+ (n=18)		FH- (n=14)		
	Errors	**Percent Accuracy**	**Errors**	**Percent Accuracy**	***p***
Color Naming	12.5 ± 9.9	79.2 ± 16.6	11.2 ± 9.3	81.3 ± 15.4	.72
Word Reading	5.7 ± 8.0	90.5 ± 13.4	3.7 ± 5.3	93.8 ± 8.9	.43
Interference	6.3 ± 5.6	82.7 ± 15.5	6.8 ± 7.3	81.1 ± 20.4	.80

Data represent mean ± SD. No significant differences ($p < .05$) were observed.

Table 3

Foci of Maximally Activated Brain Regions

		Talairach Coordinates				
Region	**BA**	**x**	**y**	**z**	**Cluster**	**SPM {t}**
Color Naming						
L. Precentral Gyrus	4	-50	-5	41	905	8.44*
R. Insula		34	15	4	549	6.56*
R. Precentral Gyrus	6	41	-5	40	788	6.19*
L. Medial Frontal Gyrus	6	-4	2	58	197	5.27*
R. Cingulate Gyrus	32	10	24	32	301	5.06*
L. Insula		-31	20	11	128	3.99
Word Reading						
R. Insula		36	21	3	707	8.05*
L. Precentral Gyrus	6	-48	-4	27	208	7.64*
R. Cingulate Gyrus	32	15	18	31	121	5.87*
L. Medial Frontal Gyrus	9	-20	24	28	47	5.33
R. Precentral Gyrus	6	45	-6	28	166	5.03
L. Insula		-36	14	-2	164	4.27
L. Medial Frontal Gyrus	6	-4	-3	60	21	4.05
Interference – Color Naming						
L. Middle Frontal Gyrus	6	-33	1	38	1408	5.77*
L. Medial Frontal Gyrus	9	-20	24	26	56	4.08
R. Precentral Gyrus	6	36	-1	30	26	3.89
R. Anterior Cingulate Gyrus	32	14	29	20	124	3.59
Interference – Word Reading						
L. Middle Frontal Gyrus	46	-40	27	17	101	3.58
L. Precentral Gyrus	6	-31	-1	38	34	3.26

L, left hemisphere; R, right hemisphere. BA, Brodmann Area. MNI coordinates transformed into Talairach Space, x=center/left of midline, y=anterior/posterior to anterior commissure, z=superior/inferior to horizontal plane through AC-PC line. SPM {t} scores significant beyond p<.001 (uncorrected) for ROI analyses are reported.

* Indicates significance at small volume corrected threshold, p<.05.

Table 4

Family History Effects: Foci of Maximally Activated Brain Regions

		Talairach Coordinates				
Region	**BA**	**x**	**y**	**z**	**Cluster**	**SPM {t}**
FH+: Word Reading						
L. Anterior Cingulate	BA24	-9	21	22	21	4.10
L. Anterior Cingulate	BA32	-7	41	12	91	3.79
R. Middle Frontal Gyrus	BA9	27	36	24	57	3.77
L. Middle Frontal Gyrus	BA46	-40	23	18	33	3.61
L. Inferior Frontal Gyrus	BA45	-44	18	11	35	3.50
R. Anterior Cingulate	BA32	14	37	13	22	3.33

L, left hemisphere; R, right hemisphere. BA, Brodmann Area. MNI coordinates transformed into Talairach Space, x=center/left of midline, y=anterior/posterior to anterior commissure, z=superior/inferior to horizontal plane through AC-PC line. SPM {t} scores significant beyond p<.001 (uncorrected) for ROI analyses are reported.

*Indicates significance at small volume corrected threshold, p<.05.

Table 5

Family History Effects: Foci of Maximally Activated Brain Regions

		Talairach Coordinates				
Region	**BA**	**x**	**y**	**z**	**Cluster**	**SPM {t}**
FH+: Interference – Color Naming						
L. Middle Frontal Gyrus	6	-35	1	38	342	5.29*
L. Insula		-40	12	17	440	4.50*
R. Anterior Cingulate Gyrus	32	14	29	20	74	4.37
L. Medial Frontal Gyrus	6	-18	9	48	35	3.90
L. Medial Frontal Gyrus	9	-20	28	25	38	3.90
R. Middle Frontal Gyrus	8	28	15	40	45	3.59
L. Insula		-36	16	-2	21	3.57
FH-: Interference – Color Naming						
L. Precentral Gyrus	6	-38	-1	32	43	3.32

L, left hemisphere; R, right hemisphere. BA, Brodmann Area. MNI coordinates transformed into Talairach Space, x=center/left of midline, y=anterior/posterior to anterior commissure, z=superior/inferior to horizontal plane through AC-PC line. SPM {t} scores significant beyond p<.001 (uncorrected) for ROI analyses are reported.

*Indicates significance at small volume corrected threshold, p<.05.

Table 6

Family History Density: Regression with Brain Activation

		Talairach Coordinates				
Region	**BA**	**x**	**y**	**z**	**Cluster**	**SPM {t}**
Positive Regression: FHD and Interference – Word Reading						
R. Anterior Cingulate Gyrus	32	6	37	11	75	5.49*
R. Middle Frontal Gyrus	6	28	5	47	603	4.84
L. Superior Frontal Gyrus	8	-3	22	51	57	4.78
R. Middle Frontal Gyrus	9	45	12	37	68	4.48
R. Precentral Gyrus	44	43	14	10	21	3.59
Negative Regression: FHD and Interference – Word Reading						
R. Superior Frontal Gyrus	6	-6	-6	65	74	4.04

L, left hemisphere; R, right hemisphere. BA, Brodmann Area. MNI coordinates transformed into Talairach Space, x=center/left of midline, y=anterior/posterior to anterior commissure, z=superior/inferior to horizontal plane through AC-PC line. SPM {t} scores significant beyond p<.001 (uncorrected) for ROI analyses are reported.

* Indicates significance at small volume corrected threshold, p<.05.

Table 7

Family History Density: Regression with Brain Activation

		Talairach Coordinates				
Region	**BA**	**x**	**y**	**z**	**Cluster**	**SPM {t}**
Positive Regression: FHD and Interference – Color Naming						
R. Middle Frontal Gyrus	8	26	11	44	1108	6.64*
L. Superior Frontal Gyrus	6	-13	15	49	198	4.83
L. Cingulate Gyrus	24	-12	11	30	59	4.60
R. Precentral Gyrus	6	39	-7	35	98	4.55
L. Insula		-38	16	14	255	4.48*
L. Middle Frontal Gyrus	9	-29	32	27	456	4.14
Negative Regression: FHD and Interference – Color Naming						
L. Superior Frontal Gyrus	6	-6	-6	67	223	5.55
L. Precentral Gyrus	6	-24	-13	64	29	4.75
R. Medial Frontal Gyrus	6	6	-27	65	47	3.54

L, left hemisphere; R, right hemisphere. BA, Brodmann Area. MNI coordinates transformed into Talairach Space, x=center/left of midline, y=anterior/posterior to anterior commissure, z=superior/inferior to horizontal plane through AC-PC line. SPM {t} scores significant beyond p<.001 (uncorrected) for ROI analyses are reported.

*Indicates significance at small volume corrected threshold, p<.05.